Andexanet Alfa (Andexxa®) for the Reversal of Direct Oral Anticoagulants

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INTRODUCTION

Oral anticoagulants are the medication of choice for the prevention of stroke in atrial fibrillation (AF) and the treatment of venous thromboembolism (VTE). Atrial fibrillation is the most common type of arrhythmia, affecting approximately 2.7 to 6.1 million people in the United States,[1] and VTE affects about another 900,000 people each year.[2] For decades, vitamin K antagonists (VKAs) have been the traditional and only oral anticoagulant option but using them can be challenging owing to nuances in monitoring, dosing, and drug interactions.[3] More recently, direct oral anticoagulants (DOACs), such as dabigatran, rivaroxaban, apixaban, edoxaban, and betrixaban, have made their way onto the market and have shown comparable or greater efficacy, a desirable safety profile, and relatively simple dosing regimens compared to the VKAs. Most importantly, they have obviated the need for frequent testing of the international normalized ratio (INR) as is required with patients taking VKAs.[4]

From 2009 to 2014, DOAC treatment visits in the United States exceeded a million patients per quarter, a figure that is similar to the number of visits by warfarin patients.[3] Although they comprise a promising group of medications, the DOACs initially had no reversal agents. Warfarin overdoses, on the other hand, are mitigated with vitamin K and clotting factor administration. Idarucizumab (Praxbind) was the first reversal agent approved in 2015 for the direct thrombin inhibitor dabigatran (Pradaxa). It is a monoclonal antibody that binds dabigatran and its metabolite, neutralizing their anticoagulant effect.[5] However, factor Xa inhibitors had no reversal agent at that time. In 2017, the American College of Cardiology released a consensus decision pathway to manage DOAC-induced bleeding: Patients taking rivaroxaban and apixaban who experienced major bleeding events could receive a four-factor prothrombin complex concentrate (4-F PCC)—Kcentra (prothrombin complex concentrate [human]).[6] However, although the agent showed correction of coagulation laboratory parameters (e.g., coagulation tests and thrombin generation), it was not consistent across all studies. The 4-F PCC proved effective for several hundred patients with DOAC-related bleeding events, but the need for a specific reversal agent remained.[6]

On May 03, 2018, the FDA approved andexanet alfa (Andexxa®), the first and only specific antidote for anticoagulation reversal in patients treated with rivaroxaban or apixaban.[7]

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INDICATION

Andexanet alfa is indicated for anticoagulation reversal in life-threatening or uncontrolled bleeding in patients treated with rivaroxaban or apixaban. The drug received accelerated approval based on studies showing the significant change in anti-factor Xa activity in healthy volunteers.[7]

MECHANISM OF ACTION

Andexanet alfa is an engineered variant of factor Xa, whose similarity to the human form allows it to bind factor Xa inhibitors with high affinity. In comparison to factor Xa, which contains serine, andexanet alfa contains alanine as its active-site residue and lacks a membrane-binding domain. These changes allow andexanet alfa to successfully bind factor Xa inhibitors without promoting further anticoagulant activity.[8] Andexanet alfa's procoagulant effects are achieved through the ability to bind and sequester factor Xa inhibitors. The drug can also bind and inhibit the activity of tissue-factor pathway inhibitor, which can increase thrombin generation and ultimately promote a procoagulant state.[7]

PHARMACOKINETICS

The pharmacokinetic properties of andexanet alfa alone have been evaluated in a phase 1, randomized, double-blind, placebo-controlled single-center study. A total of 32 healthy subjects were randomized to receive placebo or andexanet alfa in strengths of 30, 90, 300, or 600 mg. The study showed that the maximum con-

Table 1 Pharmacokinetic Parameters of Andexanet Alfa

Parameter (Mean)	30-mg Dose	90-mg Dose	300-mg Dose	600-mg Dose
Cmax (ng/mL)	3,080	10,800	52,800	93,300
Tmax (hrs)	0.21	0.23	0.26	0.51
T ½ (hrs)	7.25	7.38	7.46	6.40
Cl (L/hr)	6.30	6.24	5.13	5.18
Vss	24.95	14.80	8.27	7.82

Cmax = maximum concentration; Tmax = time when maximum concentration is reached; T ½ = half-life; Cl = clearance; Vss = volume of distribution at steady state

centration of andexanet alfa increased proportionally to the administered dose of the drug. The average volume of distribution of andexanet alfa decreased with more doses, and the clearance and half-life remained relatively similar among doses. The pharmacokinetic parameters of andexanet alfa have been collected and summarized in Table 1.[9]

In the phase 2 study, the pharmacokinetics of andexanet alfa in the presence of apixaban were evaluated. The randomized, double-blind, placebo-controlled study involved 54 healthy participants, all of whom received apixaban 5 mg twice daily for 5.5 days. The pharmacokinetics of andexanet alfa did not change significantly in the presence of apixaban and showed no significant drug–drug interactions.[9] In the ANNEXA-R trial, studies also showed minimal impact from rivaroxaban 20 mg on the pharmacokinetics of andexanet alfa.[10]

PHARMACODYNAMICS

The effects of andexanet alfa can be measured through the use of assays that measure anti-factor Xa activity, free fraction of factor Xa inhibitor, and thrombin generation. The administration of an intravenous (IV) bolus dose of andexanet alfa followed by a two-hour continuous IV infusion resulted in a rapid decrease of anti-factor Xa activity. Initial reduction in anti-factor Xa activity and regeneration of normal thrombin levels occur within two minutes of IV bolus-dose administration.[11] Reduced anti-factor Xa activity remains for up to two hours following discontinuation of the infusion. Further, andexanet alfa has the ability to inhibit tissue-factor pathway inhibitor, which is maintained for at least 22 hours following andexanet alfa's administration.[7]

DOSING/ADMINISTRATION

Andexanet alfa has two dosing regimens, a low dose and a high dose. The low-dose regimen consists of a 400-mg IV bolus given at a rate of 30 mg per minute, followed by a two-hour IV infusion at a rate of 4 mg per minute. The high dose is an 800-mg IV bolus given at a rate of 30 mg per minute, followed by a two-hour IV infusion given at a rate of 8 mg per minute. The recommended regimen for a particular patient is based on the factor Xa inhibitor used, the dose of factor Xa inhibitor, and the time since the last dose of factor Xa inhibitor. The recommendations are summarized in Table 2.[7]

Table 2 Dosing Recommendations for Andexanet Alfa

FXa Inhibitor	Last FXa Inhibitor Dose	Last FXa Inhibitor Dose < 8 Hours Prior/Unknown	Last FXa Inhibitor Dose ≥ 8 Hours Prior
Rivaroxaban	≤ 10 mg	low dose	low dose
Rivaroxaban	> 10 mg / unknown	high dose	low dose
Apixaban	≤ 5 mg	low dose	low dose
Apixaban	> 5 mg / unknown	high dose	low dose

FXa = factor Xa inhibitor

CLINICAL TRIALS

The ANNEXA-A and ANNEXA-R trials were conducted to evaluate the safety and ability of andexanet alfa to reverse the anticoagulation effects of apixaban and rivaroxaban, respectively,[10] and the results from both studies are presented in an article by Siegal et al.[10] A third trial, ANNEXA-4, evaluated the ability of andexanet alfa to reverse anticoagulation in acute major-bleeding events.[12]

ANNEXA-A and ANNEXA-R

The objective of the two parallel, randomized, double-blind, placebo-controlled trials was to determine the efficacy and safety of andexanet alfa for the reversal of anticoagulation effects from apixaban and rivaroxaban in healthy older volunteers.[10]

Volunteers ranging in age from 50 to 70 years old were randomly assigned to receive andexanet alfa or placebo in a 3:1 ratio (ANNEXA-A) or a 2:1 ratio (ANNEXA-R). Both studies were conducted in two parts: Part 1 examined a single IV-bolus dose of andexanet alfa, and Part 2 evaluated a single IV-bolus dose followed by a two-hour continuous IV infusion. Participants in ANNEXA-A received 5 mg of oral apixaban twice daily for 3.5 days in order to achieve steady state. Participants in ANNEXA-R received 20 mg of oral rivaroxaban daily for four days to achieve steady state. In both studies, an 800-mg IV bolus dose of andexanet alfa was administered a few hours after the last dose of oral anticoagulant (three hours in ANNEXA-A and four hours in ANNEXA-R), with an additional continuous infusion at a rate of 8 mg per minute during Part 2 of the study.[10]

The studies' primary endpoint was the percentage change in anti-factor Xa activity from a baseline established before the administration of andexanet alfa. Anti-factor Xa activity was monitored at two minutes and five minutes after the bolus dose was administered, and the smaller of the two values was recorded. In Part 2, anti-factor Xa activity was monitored 10 minutes prior to the end of the infusion and five minutes after the infusion; the smaller of the two values was recorded.

A bolus dose of andexanet alfa significantly reduced anti-factor Xa activity compared with placebo in both the apixaban study (mean [± standard deviation [SD] reduction, 94 ± 2% vs. 21 ± 9%; $P < 0.001$) and the rivaroxaban study (92 ± 11% vs. 18 ± 15%; $P < 0.001$). In Part 2 of the studies, the results also showed a significant reduction in anti-factor Xa activity in the apixaban study (92 ± 3% vs. 33 ± 6%; $P < 0.001$) and the rivaroxaban study (97 ± 2% vs. 45 ± 12%; $P < 0.001$).[10] The effects of andexanet alfa in both parts of the trial lasted for approximately one to two hours following administration of the bolus dose (trial Part 1) or after completion of the infusion (trial Part 2).[10]

Additional secondary efficacy endpoints included the percentage of volunteers with a reduction of 80% or greater in anti-factor Xa activity from baseline, and the change in unbound factor Xa inhibitor plasma concentration. All participants (100%) in both studies who were treated with andexanet alfa had a reversal of at least 80% of anti-factor Xa activity, whereas none of the placebo patients had a reversal of 80% of anti-factor Xa activity ($P < 0.001$). Andexanet alfa was also found to reduce the unbound inhibitor concentration in both the apixaban and rivaroxaban study groups. For patients receiving apixaban, andexanet alfa significantly reduced the mean unbound concentration compared

to patients receiving placebo (reduction, 9.3 ng/ml vs. 1.9 ng/ml). For patients receiving rivaroxaban, andexanet alfa also significantly reduced the mean unbound concentration compared to those receiving placebo (reduction, 23.4 ng/ml vs. 4.2 ng/ml). After the end of the infusion, unbound factor Xa inhibitor concentrations returned to approximately those seen in the placebo group within one to three hours.[10]

Safety

There were no serious adverse events reported in either study and all reported side effects were mild. Only one volunteer, who had a history of hives, developed hives during an andexanet alfa infusion; this was immediately mitigated with diphenhydramine and by discontinuing the infusion. No patient developed antibodies to factor Xa or X, and 2% and 17% of patients in the apixaban and rivaroxaban studies, respectively, developed non-neutralizing antibodies. However, these titers were generally low, and all results indicated a lack of immunogenicity with andexanet alfa.[10]

ANNEXA-4

The ANNEXA-4 trial was a multicenter, prospective, open-label, single-group study evaluating 352 patients who had experienced an acute major bleeding episode within 18 hours of receiving a factor Xa inhibitor.[12]

Patients eligible to participate included those who were at least 18 years old and who had been administered a factor Xa inhibitor within the previous 18 hours. Exclusion criteria included having surgery scheduled within 12 hours of presentation, intracranial hemorrhage (in a patient with a Glasgow Coma Scale score < 7), and having experienced a major thrombotic event two weeks prior to study commencement. Patients who had an acute bleeding event would receive an andexanet alfa bolus dose followed by a two-hour infusion of the drug. All patients who received andexanet alfa were included in the safety analysis, but only those who had a baseline anti-factor Xa activity of 75 ng/ml or greater were included in the efficacy analysis. The two co-primary outcomes of the study were the percentage change in anti-factor Xa activity and the rate of excellent or good hemostatic efficacy. An independent adjudication committee reviewed each case to determine hemostatic efficacy and the eligibility of each patient for the study.[12]

Table 3 Definitions of Hemostasis Assessment in ANNEXA-4 Trial

Bleeding Event	Excellent Hemostasis	Good Hemostasis
Intracerebral Hemorrhage	≤ 20% increase in volume from baseline at both 1 hour and 12 hours after andexanet infusion	≤ 35% increase in volume from baseline at both 1 hour and 12 hours after andexanet infusion
Non-Visible Bleeds	≤ 10% decrease in the correct hemoglobin and hematocrit at 12 hours	≤ 20% decrease in the correct hemoglobin and hematocrit at 12 hours
Visible Bleeds	Cessation of bleeding within 1 hour of infusion	Cessation of bleeding within 4 hours of infusion

Patients who received andexanet alfa treatment were given a 400-mg bolus dose and a 480-mg infusion dose if a factor Xa inhibitor was given more than seven hours before presentation, or an 800-mg bolus dose followed by a 960-mg infusion dose if the inhibitor was given seven hours or less before presentation. Patients were then assessed at 15 minutes, four hours, eight hours, and 12 hours after the end of the infusion. In addition, there was a follow-up on Days 3 and 30. At each assessment within the first 12 hours following infusion, factor Xa inhibitor concentration and anti-factor Xa activity were recorded. Hemostatic efficacy was determined by the criteria in Table 3.[12]

Of the patients included in the efficacy arm, 100 were taking rivaroxaban. After the administration of a bolus and infusion dose of andexanet alfa, the median anti-factor Xa activity fell from 211.8 ng/ml to 16.5 ng/ml, a 90% decrease from baseline (95% confidence interval [CI], 87–93). However, four hours after the infusion, the median level was 121.7 ng/ml, a 42% decrease from baseline (95% CI, 36–45). In the 134 patients receiving apixaban, the median value of anti-factor Xa decreased from 149.7 ng/ml to 11.5 ng/ml, a 92% decrease from baseline (95% CI, 91–93). Four hours after infusion, the median value was 97.2 ng/ml, a 32% decrease from baseline (95% CI, 29–38). Of the 254 participants in the efficacy arm, 249 were evaluated for hemostatic efficacy; 204 were determined to have excellent or good hemostasis (171 excellent, 33 good) 12 hours after the infusion.[12]

Safety

Among the 352 patients included in the safety arm, there were no reported infusion reactions, antibody formation to factors Xa or X, or neutralizing antibodies to andexanet alfa. Thrombotic events occurred in 12 patients, some of whom experienced multiple events. There were 49 deaths, 14 of which were non–cardiovascular-related events.[12]

COST CONSIDERATIONS

According to the American College of Cardiology, 4-F PCC (Kcentra) is the product of choice to mitigate bleeding events caused by apixaban and rivaroxaban. The average wholesale price (AWP) of the agent is $2.90 per unit,[13] and as it is dosed at 50 units/kg, treating a patient who weighed 100 kg would cost approximately $14,500. Andexanet alfa is dosed at a total (bolus plus infusion) of either 880 mg or 1,760 mg, based on the specific anticoagulant used, the dose, and the time since last dose. Andexanet alfa is sold in 100-mg and 200-mg vials; the 100-mg AWP is $3,300 and the 200-mg AWP, $6,600. The cost of a low dose (880 mg) is approximately $29,700 and a high dose (1,760 mg), approximately $59,400.[13]

CONCLUSION

Andexanet alfa is the first FDA-approved agent for the reversal of anticoagulation in patients treated with apixaban or rivaroxaban. This agent dramatically decreases the anti-factor Xa activity within two minutes of administration and it has received an accelerated approval from the FDA. Despite its relatively high cost, andexanet alfa has shown promising results and potential in managing life-threatening bleeds for patients who are taking DOACs.

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